REMARKS/ARGUMENTS

Reexamination and reconsideration of the present application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the remarks that follow.

Independent claims 1, 27, 38, and 51 have been amended for to recite that the formulation is adapted for localized delivery to the lungs of a mammal via oral inhalation such that absorption of the hypertension reducing agent into the systemic blood circulation is less than when the hypertension reducing agent is administered intravenously or orally to the gastrointestinal tract. Support for these amendments can be found at least on paragraphs [0011], [0012], and [0036] of the published application (i.e. U.S. Publication No. 2004/0265238). No new matter has been entered.

I. Currently Claimed Invention

The present invention is premised, in part, on the known systemic hypertension reducing effects of ACEIs, ARBs, beta-blockers, calcium-channel blockers or vasodilators to treat pulmonary hypertension. The currently claimed formulations represent an improvement over conventional means for treating pulmonary hypertension, because the claimed formulations are adapted for localized delivery to the user's lungs such that a reduced amount of active is absorbed into the systemic blood circulation as compared to when the hypertension reducing agent is administered intravenously or orally to the gastrointestinal tract. As such, the currently claimed formulations can be administered in lower doses and reduce the level of side effects associated with systemic delivery as known in the art.

II. Rejections under 35 U.S.C. §112

Claims 1-2, 12-16, 21, 25-30, 32, 34, 38-40, 51-54, 57-64 and 66-71 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Office appears to argue that the term "reduced level" in each of the independent claims is not supported since the specification does not recite "any level of active agent in the blood circulation". See page 3 of the Office Action.

Applicant disagrees with the Office's argument that the claims fail to comply with the written description. To expedite prosecution, however, Applicant has amended independent claims 1, 27, 38, and 51 be removing reference to a "reduced level" and also the term "systemic effects". In particular, each independent claim has been amended to recite that the formulation is adapted for localized delivery to the lungs of a mammal such that absorption of the hypertension reducing agent into the systemic blood circulation is less than when the hypertension reducing agent is administered intravenously or orally to the gastrointestinal tract. Applicant respectfully submits that for at least the foregoing claim amendments, the rejections under 35 U.S.C. §112 have been overcome and requests withdrawal thereof.

III. Rejections under 35 U.S.C. §103

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit ' 'no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases.'' *Id.* at ___, 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* at ___, 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that '' '[R]ejections on

obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' '' *Id* . at ___, 82 USPQ2d at 1396.

1.

Claims 1-2, 12-16, 21, 25-30, 32, 34, 38-40, 51-54, 57-64, 66-69 and 71 stand rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,554,610 to Williams et al (hereinafter "Williams"), as evidenced by Newman (Aerosol deposition considerations in inhalation therapy, CHEST, 1985, in view of U.S. Publication No. 2001/0031738 to Schwarz (hereinafter "Schwarz") and further in view of U.S. Patent No. 4,885,305 to Mead et al. (hereinafter "Mead"). Applicant respectfully traverses this rejection.

Applicant submits that none of the currently pending claims are obviated by Williams (as evidenced by Newman), Schwarz, Mead, or any combination thereof. For instance, each of the cited references, alone or in any combination, fail to teach, suggest, or render predictable all currently claimed elements. In particular, each of the cited references, alone or in any combination, fail to teach, suggest, or render predictable any of the following: (1) a formulation adapted for localized delivery to the lungs having a reduced concentration of a calcium channel blocker comprising about 0.001 to about 0.50 mg/ml; (2) a formulation adapted for localized delivery via oral inhalation to the lungs of a mammal such that absorption of the hypertension reducing agent into the systemic blood circulation is less than when the hypertension reducing agent is administered intravenously or orally to the gastrointestinal tract.

Williams is generally directed to methods of treating disorders associated with pulmonary hypertension by administering a given dose (mg) of a vasodilator, ganglion blocker, sympathetic nerve blocker or calcium channel blocker. Williams teaches that a "unit dose will normally contain 0.01 to 50 mg for example 0.01 to 10 mg, of the Compound, or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day such that the total daily dose is normally in the range of 0.0001 to 1 mg/kg." See column 2, lines 20-29. Williams provides

that such unit doses can be inhaled. The Office acknowledges that Williams does not disclose the recited pH levels, an isotonic formulation, or the addition of complexing agents.

As set forth in MPEP 2144.05, when a prior art reference discloses a range that is so broad as to encompass an excessively large number of possible compositions, the situation can be analogous to the obviousness of a species when the prior art broadly discloses a genus. As discussed below, Williams range provides at least 10,000 different levels for one skilled in the art to select. Accordingly, the present situation is clearly analogous to that of the obviousness of a species when the prior art broadly discloses a genus.

As discussed in MPEP 2144.08, "the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). In the present case, the fact that Williams may disclose a range of concentrations that overlaps or encompasses the currently recited range is not sufficient to establish a *prima facie* case of obviousness. Of particular interest, Applicant notes that Williams fails to expressly teach any particular reason to select the claimed concentration range.

As such, Williams is silent regarding any concentration range of a calcium channel blocker, let alone a range specifically of 0.001 to 0.50 mg/ml as recited in currently amended independent claims 1, 27, 38, and 51. The daily dosage teaching of Williams, namely the administration of 0.0001 to 1 mg/kg per day includes a nearly infinite number of possible dosages, which in turn leads to an even greater number of potential concentrations. For instance, the lowest dosage range disclosed in Williams is 4 orders of magnitude lower than that of the highest dosage. Due to the breadth of such a teaching, Williams fails to provide any particular teaching that would provide the skilled artisan a reasonable basis for specifically selecting and preparing a formulation having the currently claimed concentration range from the nearly infinite possibilities referenced by Williams. For instance, when taken in 0.0001 increments (since this is the lower limit of Williams range), there are 10,000 different levels for one skilled in the art to select. Williams provides no teaching that would incite one skilled in the art to select any particular concentration range.

As such, one skilled in the art would have no rational basis to select the currently claimed range from the nearly infinite possibilities encompassed within Williams. Additionally, the vast number of possibilities makes it impossible for one skilled in the art to experimentally try every possible (or even most) dosage levels, much less formulate specific concentrations. Therefore, Williams does not teach, suggest or render predictable the claimed concentration range. See MPEP 2144.05 and 2144.08.

Additionally, Williams fails to teach, suggest or render predictable a formulation adapted for localized delivery via oral inhalation to the lungs of a mammal such that absorption of the hypertension reducing agent into the systemic blood circulation is less than when the hypertension reducing agent is administered intravenously or orally to the gastrointestinal tract. Williams is silent about such formulations and methods of treatment wherein a reduced level of active agent can be beneficially utilized. Applicant notes that inhaled snuffs or aerosols deposited in the throat, mouth, nasal mucosa, etc. can absorb into the systemic blood circulation system. Consequently, these formulations require an increased dosage of active agent since the drug will be transported throughout at least a section of the body prior to reaching the constricted arteries within the lung. As such, Williams not only fails to teach, suggest, or render predictable the currently claimed concentration range, but also the localized delivery of such a formulation to the lungs (i.e. lung vasculature), let alone via oral inhalation.

As referenced above, Williams is silent regarding a formulation adapted for localized delivery via oral inhalation to the lungs of a mammal such that absorption of the hypertension reducing agent into the systemic blood circulation is less than when the hypertension reducing agent is administered intravenously or orally to the gastrointestinal tract as recited in independent claims 1, 27, 38 and 51. Similarly, Williams is silent regarding methods of treating pulmonary hypertension by locally delivering a calcium channel blockers to the lungs (i.e. to target the blood vessels connected and within the lung) of a patient via oral inhalation. In light of this silence, the skilled artisan would have no basis to specifically targeting the deep lungs of a patient as opposed to the throat, mouth or nasal cavities. Additionally, in view of Williams extensive teachings related to elixirs, syrups and tablets, the skilled artisan would have no reasonable basis for modifying the teachings of Williams to avoid systemic absorption by

targeting the deep lungs of a patient for depositing a calcium channel blocker. For instance, the elixirs, syrups and tablets taught by Williams certainly cannot be used for localized delivery to the lungs via oral inhalation as currently claimed. Accordingly, Williams does not teach, suggest, or render predictable all elements of the currently claimed invention.

The Office cites Newman for the apparent proposition that other agents have been administered via inhalation therapy. Newman discusses the administration of beta-agonist by inhalation and the mechanics of deposition of aerosols containing the same. Newman, however, is silent about calcium channel blockers, the claimed concentration range, and a formulation comprising a calcium channel blocker adapted for localized delivery via oral inhalation to the lungs of a mammal such that absorption of the hypertension reducing agent into the systemic blood circulation is less than when the hypertension reducing agent is administered intravenously or orally to the gastrointestinal tract. As such, Newman does not cure any of the noted deficiencies of Williams.

The Office cites Schwarz for support that it is well known in the art to utilize an isotonic formulation having a pH from 3 to 8 for formulations suitable for inhalation or nasal administration. Schwarz is directed to formulations for inhibiting endothelial-monocyte activating polypeptide II (EMAP II) by administering a compound that "inhibits EMAP II activity, including compounds that specifically bind to EMAP II (e.g., an antibody), compounds that downregulate EMAP II expression (e.g., an antisense oligonucleotide), or EMAP II receptor antagonists." Schwarz teaches that the compositions can be made isotonic and a pH of around 6. The Office relies on Mead for teaching a complexing agent.

Schwarz and Mead, however, each fail to cure the deficiencies of Williams discussed above.

Since Williams (as evidenced by Newman), Schwarz, Mead or any combination thereof all suffer from the same deficiencies, the cited references alone or in any combination fail to teach, suggest, or render predictable all of the currently claimed elements. Applicant submits that the Office has not established a *prima facie* case of obviousness. Therefore, Applicant submits that this rejection has been overcome and requests withdrawal of this rejection.

2.

Claim 70 stands rejected under 35 U.S.C. §103(a) as being obvious over Williams as evidenced by Newman, in view of Schwarz, Mead and further in view of U.S. Patent No. 5,804,212 to Illum (herinafter "Illum"). Applicant respectfully traverses this rejection. The Office cites Illum for teaching a lecithin.

Illum is directed to nasal formulations (not adapted for localized delivery to the lungs, much less via oral inhalation) including microspheres. These formulations are administered to the **nasal cavity for delivery of drugs that will act within the systemic blood circulation (contrary to the currently claimed invention).**

Furthermore, Illum does not provide any teaching that would suggest the addition of alginates to inhalable formulation adapted for localized delivery to the lungs of a mammal via oral inhalation. In view of this silence, one skilled in the art would have no rational basis for preparing a formulation for delivery to the lungs of a mammal via oral inhalation as suggested by the Office. Any such suggestion would appear to be based on Applicant's present disclosure.

In this regard, and as previously discussed, all currently pending claims, are not obviated by Kiechel, Williams and Schwarz, either separately or in combination, and Illum does not remedy any of the noted deficiencies in this regard. Applicant thus submits that these rejections have been overcome and requests withdrawal thereof.

IV. Provisional Double Patenting Rejection

Claims 1, 2, 12-16, 21, 25-30, 32, 38-40 and 51-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting of copending application Serial No. 11/316,458. Since this is a provisional rejection and the Office has not indicated the allowance of any of the pending claims, Applicant will not file a terminal disclaimer at this time. Upon indication of allowable subject matter, Applicant will submit a terminal disclaimer to overcome the rejection.

Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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